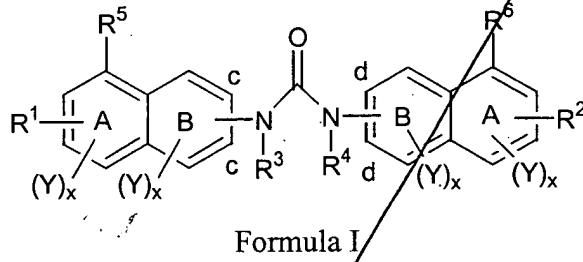


We claim:

1. A method of treating a metabolic disorder in a person induced by treatment of the person with an HIV protease inhibitor, comprising administering to the person a therapeutically effective dose of an insulin receptor-activating compound that is not insulin, or a pharmaceutically acceptable salt thereof.
2. The method of claim 1, where the metabolic disorder induced by treatment with an HIV protease inhibitor is selected from the group consisting of insulin resistance, hyperglycemia, diabetes, ketoacidosis, lipodystrophy, and hypertriglyceridemia.
3. The method of claim 1, where the insulin receptor-activating compound is a compound of Formula I



wherein:

$R^1$  and  $R^2$  are substituents on the A ring and are, independently,  $-SO_2NR^7_2$ ,  $-C(O)NR^7_2$ ,  $-NR^7SO_2R^7$ ,  $-NR^7C(O)R^7$ ,  $-SO_2OR^7$ ,  $-C(O)OR^7$ ,  $-OSO_2R^7$ , or  $-OC(O)R^7$ ,

$R^3$  and  $R^4$  are, independently, hydrogen or lower alkyl, or  $R^3$  and  $R^4$  together are  $-(CH_2)_2-$ ,  $-(CH_2)_3-$ , or  $-(CH_2)_4-$ ,

$R^5$  and  $R^6$  are, independently, hydrogen, lower alkyl, substituted lower alkyl, cyano, halo, nitro,  $-SR^8$ ,  $-C(O)R^8$ ,  $-SO_2OR^8$ ,  $-OSO_2R^8$ ,  $-SO_2NR^8_2$ ,  $-NR^8SO_2R^8$ ,  $-OC(O)R^8$ ,  $-C(O)OR^8$ ,  $-C(O)NR^8_2$ ,  $-NR^8C(O)R^8$ ,  $-OR^8$ , or  $-NR^8_2$ ,

each  $R^7$  and  $R^8$  is, independently, hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, aryl(lower)alkyl, substituted

Sub  
Alt  
Smt

aryl(lower)alkyl, heteroaryl(lower)alkyl, substituted heteroaryl-(lower)alkyl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl,

each Y is a non-interfering substituent,

each  $x$  is, independently, 0, 1 or  $\frac{1}{2}$ , and

the urea linker connects a carbon which is designated c with a carbon which is designated d,

or a pharmaceutically acceptable salt thereof, optionally in the form of a single stereoisomer or mixture of stereoisomers thereof.

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4. The method of claim 3, wherein no Y is linked to a naphthalene ring via an azo linkage in the compound.

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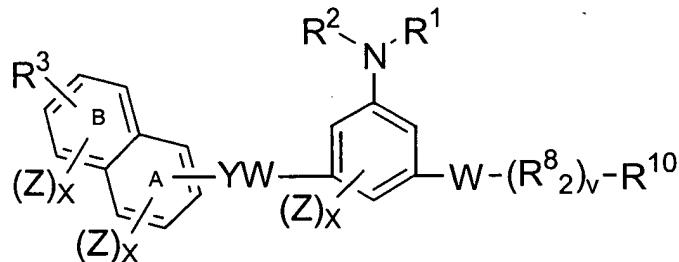
5. The method of claim 3, wherein, where  $R^1$  and  $R^2$  are both  $-SO_2OH$ ,  
(i) no  $Y$  is  $-SO_2OH$ ;

(ii) neither  $R'$  nor  $R''$  is  $-SO_2OR''$  or  $-OSO_2R''$ ; and

(iii) where no  $(Y)_x$  is  $(Y')_{x'}$ , wherein  $x'$  is 1 or 2 and  $Y'$  is a halo radical,  $R^{\circ}$  and  $R^{\bullet}$  are not both selected from the group consisting of hydroxy and hydrogen.

20

6. The method of claim 1, where the insulin receptor-activating compound is a compound of Formula II



## Formula II

wherein:

25

$R^1$  and  $R^2$  are, independently, hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl,  $-C(O)R^4$ ,  $-C(O)OR^4$ ,  $-C(O)NR^4R^5$ ,  $-S(O)_2R^4$ ,

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-S(O)<sub>2</sub>OR<sup>4</sup>, heteroaryl, substituted heteroaryl, heterocyclyl, substituted heterocyclyl, aryl(lower)alkyl, substituted aryl(lower)-alkyl, heteroaryl(lower)alkyl, substituted heteroaryl(lower)alkyl, or lower alkenyl, or R<sup>1</sup> and R<sup>2</sup> together with the conjoining nitrogen are C<sub>3</sub>-C<sub>9</sub> heteroaryl, C<sub>3</sub>-C<sub>5</sub> heterocyclyl, or -NO<sub>2</sub>,

5 R<sup>3</sup> is a substituent on the B ring and is -SO<sub>2</sub>OR<sup>6</sup>, -C(O)OR<sup>6</sup>, -SO<sub>2</sub>NR<sup>6</sup><sub>2</sub>, -C(O)NR<sup>6</sup><sub>2</sub>, or tetrazole;

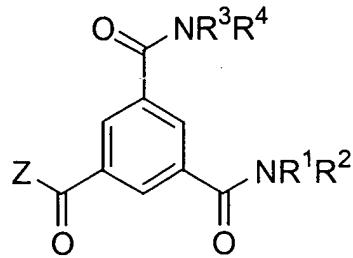
each linker -WY- between the naphthyl and phenyl intersects the A ring on the naphthyl and is, independently, -C(O)NR<sup>7</sup>-, -NR<sup>7</sup>C(O)-, -C(O)O-, -OC(O)-, -CH=CH-, -NR<sup>7</sup>CH<sub>2</sub>-, -CH<sub>2</sub>NR<sup>7</sup>-, -NR<sup>7</sup>C(O)NR<sup>7</sup>-,  
10 -NR<sup>7</sup>C(O)O-, -OC(O)NR<sup>7</sup>-, -NR<sup>7</sup>SO<sub>2</sub>O-, -OSO<sub>2</sub>NR<sup>7</sup>-, -OC(O)O-, -SO<sub>2</sub>NR<sup>7</sup>-, -NR<sup>7</sup>SO<sub>2</sub>-, -OSO<sub>2</sub>-, or -SO<sub>2</sub>O-,  
each R<sup>4</sup> and R<sup>5</sup> is, independently, hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, aryl(lower)alkyl, substituted aryl(lower)alkyl, substituted heteroaryl, heteroaryl, heteroaryl(lower)alkyl, substituted heteroaryl(lower)alkyl, heterocyclyl, substituted heterocyclyl, or lower alkenyl,  
15 each R<sup>6</sup> and R<sup>7</sup> is, independently, hydrogen or lower alkyl,  
each R<sup>8</sup> is, independently, hydrogen, lower alkyl, substituted lower alkyl, aryl(lower)alkyl, substituted aryl(lower)alkyl, substituted heteroaryl, heteroaryl, heteroaryl(lower)alkyl, substituted heteroaryl(lower)alkyl, heterocyclyl, substituted heterocyclyl, lower alkenyl, nitro, halo, cyano,  
20 -OR<sup>9</sup>, -SR<sup>9</sup>, -C(O)R<sup>9</sup>, -OC(O)R<sup>9</sup>, -C(O)OR<sup>9</sup>, -NR<sup>9</sup><sub>2</sub>, -C(O)NR<sup>9</sup><sub>2</sub>, -NR<sup>9</sup>C(O)R<sup>9</sup>, -OSO<sub>2</sub>R<sup>9</sup>, -SO<sub>2</sub>OR<sup>9</sup>, -SO<sub>2</sub>NR<sup>9</sup><sub>2</sub>, or -NR<sup>9</sup>SO<sub>2</sub>R<sup>9</sup>,  
each R<sup>9</sup> is, independently, hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heteroaryl(lower)alkyl, substituted heteroaryl(lower)alkyl, heterocyclyl, substituted heterocyclyl, aryl(lower)alkyl, or substituted aryl(lower)alkyl,  
25 each Z is a non-interfering substituent,

30

each x and v is, independently, 0, 1, 2 or 3, and  
R<sup>10</sup> is aryl, substituted aryl, heteroaryl, or substituted heteroaryl,  
or a pharmaceutically acceptable salt thereof, optionally in the form of a single  
stereoisomer or mixture of stereoisomers thereof.

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7. The method of claim 1, where the insulin receptor-activating compound is a  
compound of Formula III



Formula III

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wherein:

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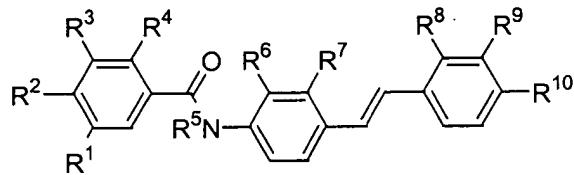
R<sup>1</sup> and R<sup>2</sup> are, independently, hydrogen, lower alkyl, substituted lower alkyl,  
aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl,  
substituted heterocyclyl, aryl(lower)alkyl, substituted aryl(lower)-alkyl,  
heteroaryl(lower)alkyl, substituted heteroaryl(lower)alkyl, or lower  
alkenyl, or R<sup>1</sup> and R<sup>2</sup> together with the conjoining nitrogen are C<sub>3</sub>-C<sub>9</sub>  
heteroaryl, or C<sub>3</sub>-C<sub>5</sub> heterocyclyl,

Z is OH, halo, OR<sup>1</sup> or NR<sup>1</sup>R<sup>2</sup>,

or a pharmaceutically acceptable salt thereof, optionally in the form of a single  
stereoisomer or mixture of stereoisomers thereof.

20

8. The method of claim 1, where the insulin receptor-activating compound is a compound of Formula IV



Formula IV

5 wherein

R<sup>1</sup>, R<sup>3</sup>, and R<sup>4</sup> are, independently, hydrogen, lower alkyl, substituted lower alkyl, halo, hydroxyl, substituted alkyloxy, carboxyl, -NR<sup>11</sup>R<sup>12</sup>, or -C(O)N R<sup>11</sup>R<sup>12</sup>,

10 R<sup>2</sup> is hydrogen, lower alkyl, substituted alkyl, halo, hydroxyl, alkoxy, substituted alkyloxy, carboxyl, -NR<sup>11</sup>R<sup>12</sup>, -NR<sup>11</sup>C(O)R<sup>12</sup>, or -C(O)NR<sup>11</sup>,

R<sup>5</sup> is hydrogen, lower alkyl, substituted lower alkyl, or aryl,

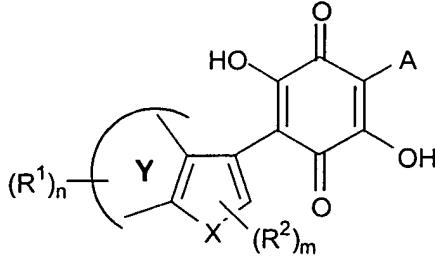
R<sup>6</sup> and R<sup>7</sup> are, independently, hydrogen or carboxyl,

15 R<sup>8</sup> and R<sup>9</sup> are, independently, hydrogen, lower alkyl, substituted lower alkyl, halo, hydroxyl, alkoxy, carboxyl, -NR<sup>11</sup>R<sup>12</sup>, or -C(O)NR<sup>11</sup>R<sup>12</sup>,

R<sup>10</sup> is lower alkyl, substituted lower alkyl, halo, carboxyl, -C(O)NR<sup>11</sup>R<sup>12</sup>,

20 R<sup>11</sup> and R<sup>12</sup> are, independently, hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, aryl(lower)alkyl, substituted aryl(lower)alkyl, heteroaryl-(lower)alkyl, -substituted heteroaryl(lower)alkyl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl-C(O)-aryl, or aryl, or a pharmaceutically acceptable salt thereof, optionally in the form of a single stereoisomer or mixture of stereoisomers thereof.

9. The method of claim 1, where the insulin receptor-activating compound is a compound of Formula V



Formula V

5

wherein

Ring Y represents a 5-6-membered aryl or heteroaryl fused ring, which is optionally substituted with 1-4 groups selected from R<sup>1</sup>;

X represents O, S(O)<sub>m</sub> or N, wherein m is 0, 1 or 2;

A represents a member selected from the group consisting of:

10

(a) a 6-10-membered mono-or bicyclic aryl group,

(b) a 5-6-membered isolated monocyclic heteroaryl group,

(c) a 9-10-membered bicyclic heteroaryl group, attachment to which is through a 6-membered ring, or

(d) an 8-membered bicyclic heteroaryl group, the heteroaryl groups having 1-4

15

heteroatoms selected from O, S(O)<sub>m</sub> and N, said aryl and heteroaryl groups being optionally substituted with 1-3 R<sup>1</sup> groups;

R<sup>1</sup> is independently selected from:

halo, -OH, -C<sub>1-12</sub>alkyl(R<sup>2</sup>)<sub>3</sub>, -C<sub>2-10</sub>alkenyl(R<sup>2</sup>)<sub>3</sub>, -C<sub>2-10</sub>alkynyl(R<sup>2</sup>)<sub>3</sub>, -C<sub>6-10</sub>aryl(R<sup>2</sup>)<sub>3</sub>,

-heteroaryl(R<sup>2</sup>)<sub>3</sub>, -heterocyclyl(R<sup>2</sup>)<sub>3</sub>, -NH<sub>2</sub>, -NHC<sub>1-6</sub>alkyl(R<sup>2</sup>)<sub>3</sub>,

-N(C<sub>1-6</sub>alkyl(R<sup>2</sup>)<sub>3</sub>)<sub>2</sub>, -N<sub>3</sub>, -OC<sub>1-6</sub>alkyl(R<sup>2</sup>)<sub>3</sub>, -S(O)<sub>m</sub>H, S(O)<sub>m</sub>C<sub>1-6</sub>alkyl(R<sup>2</sup>)<sub>3</sub>,

-CHO, -C(O)C<sub>1-6</sub>alkyl(R<sup>2</sup>)<sub>3</sub>, -CO<sub>2</sub>H, -C(O)OC<sub>1-6</sub>alkyl(R<sup>2</sup>)<sub>3</sub>,

-C(O)SC<sub>1-6</sub>alkyl(R<sup>2</sup>)<sub>3</sub>, -C(O)NH<sub>2</sub>, -C(O)NHC<sub>1-6</sub>alkyl(R<sup>2</sup>)<sub>3</sub>,

-NHC(O)C<sub>1-6</sub>alkyl(R<sup>2</sup>)<sub>3</sub>, -S(O)<sub>m</sub>NH<sub>2</sub>, -NHS(O)<sub>m</sub>C<sub>1-6</sub>alkyl(R<sup>2</sup>)<sub>3</sub>,

-S(O)<sub>m</sub>NHC<sub>1-6</sub>alkyl(R<sup>2</sup>)<sub>3</sub> and -S(O)<sub>m</sub>N(C<sub>1-6</sub>alkyl(R<sup>2</sup>)<sub>3</sub>)<sub>2</sub>

wherein m is 0, 1, or 2;

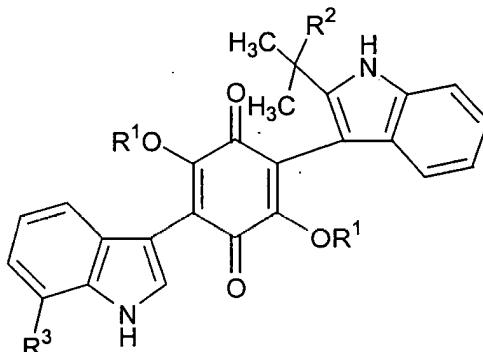
R<sup>2</sup> is independently selected from:

H, OH, halo, -C<sub>1-4</sub> alkyl, -C<sub>2-4</sub> alkenyl, -C<sub>2-4</sub> alkynyl, -CF<sub>3</sub>, -OCF<sub>3</sub>, -NO<sub>2</sub>, -N<sub>3</sub>, -CHO,  
 -OC<sub>1-6</sub> alkyl, -S(O)<sub>m</sub>C<sub>1-6</sub>alkyl, -NH<sub>2</sub>, -NHC<sub>1-6</sub>alkyl, -N(C<sub>1-6</sub>alkyl)<sub>2</sub>,  
 -C(O)C<sub>1-6</sub>alkyl, -CO<sub>2</sub>H, -CO<sub>2</sub>C<sub>1-6</sub>alkyl, -C(O)NH<sub>2</sub>, -C(O)NHC<sub>1-6</sub>alkyl,  
 -C(O)N(C<sub>1-6</sub>alkyl)<sub>2</sub>, -OC(O)C<sub>1-6</sub>alkyl, -NHC(O)C<sub>1-6</sub>alkyl, -S(O)<sub>m</sub>NH<sub>2</sub>,  
 -S(O)<sub>m</sub>NHC<sub>1-6</sub>alkyl, -S(O)<sub>m</sub>(C<sub>1-6</sub>alkyl)<sub>2</sub>, aryl, heteroaryl and heterocyclyl

wherein m is 0,1, or 2,

or a pharmaceutically acceptable salt thereof, optionally in the form of a single  
 stereoisomer or mixture of stereoisomers thereof.

10. The method of claim 1, where the insulin receptor-activating compound is a  
 compound of Formula VI



15 Formula VI

wherein

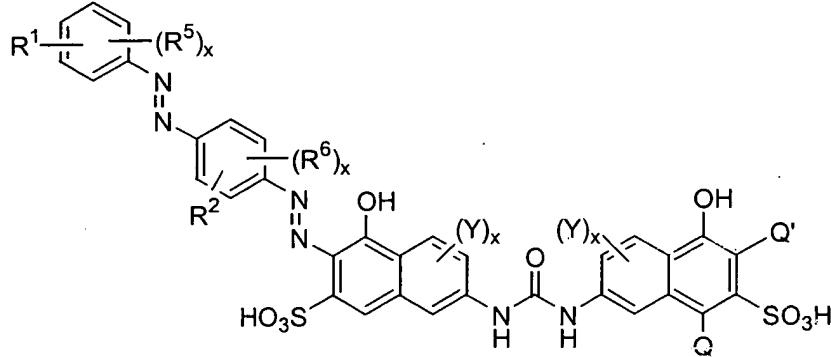
R<sup>1</sup> is hydrogen, or methyl

R<sup>2</sup> is -CH<sub>2</sub>CH<sub>3</sub> or -CH=CH<sub>2</sub>

R<sup>3</sup> is -CH=CH-C(CH<sub>3</sub>)=CH<sub>2</sub>; CH<sub>2</sub>-CH=C(CH<sub>3</sub>)<sub>2</sub> or -CH<sub>2</sub>-CH<sub>2</sub>-CH=C(CH<sub>3</sub>)<sub>2</sub>,

20 or a pharmaceutically acceptable salt thereof, optionally in the form of a single  
 stereoisomer or mixture of stereoisomers thereof

11. The method of claim 1, where the insulin receptor-activating compound is a compound of Formula VII

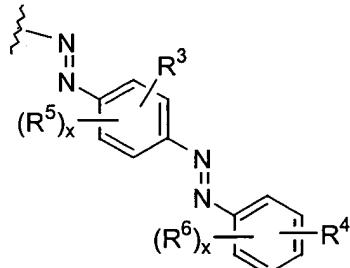


Formula VII

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wherein

Q and Q' are either hydrogen or



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R<sup>1</sup> and R<sup>2</sup> are, independently, -SO<sub>2</sub>NR<sup>7</sup><sub>2</sub>, -C(O)NR<sup>7</sup><sub>2</sub>, -NR<sup>7</sup>SO<sub>2</sub>R<sup>7</sup>, -SO<sub>2</sub>OR<sup>7</sup>, -C(O)OR<sup>7</sup>, -PO<sub>3</sub>R<sup>7</sup><sub>2</sub>, or tetrazolyl,

15 R<sup>3</sup> and R<sup>4</sup> are, independently, -SO<sub>2</sub>NR<sup>7</sup><sub>2</sub>, -C(O)NR<sup>7</sup><sub>2</sub>, -NR<sup>7</sup>C(O)R<sup>7</sup>, -SO<sub>2</sub>OR<sup>7</sup>, -C(O)OR<sup>7</sup>, -PO<sub>3</sub>R<sup>7</sup><sub>2</sub>, or tetrazolyl,

R<sup>5</sup> and R<sup>6</sup> are, independently, hydrogen, lower alkyl, substituted lower alkyl, cyano, halo, nitro, -SR<sup>8</sup>, -C(O)R<sup>8</sup>, -SO<sub>2</sub>OR<sup>8</sup>, -OSO<sub>2</sub>R<sup>8</sup>, -SO<sub>2</sub>NR<sup>8</sup><sub>2</sub>, -NR<sup>8</sup>SO<sub>2</sub>R<sup>8</sup>, -OC(O)R<sup>8</sup>, -C(O)OR<sup>8</sup>, -C(O)NR<sup>8</sup><sub>2</sub>, -NR<sup>8</sup>C(O)R<sup>8</sup>, -OR<sup>8</sup>, or -NR<sup>8</sup><sub>2</sub>,

15

each R<sup>7</sup> and R<sup>8</sup> is, independently, hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, aryl(lower)alkyl, substituted aryl(lower)alkyl, heteroaryl(lower)alkyl, substituted heteroaryl(lower)alkyl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl,

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each Y is a non-interfering substituent, and  
each x is, independently, 0, 1 or 2,  
or a pharmaceutically acceptable salt thereof, optionally in the form of a single  
stereoisomer or mixture of stereoisomers thereof.

5

12. The method of claim 1, further comprising administering a therapeutically effective amount of an additional form of treatment for insulin resistance, hyperglycemia, diabetes, ketoacidosis, lipodystrophy, or hypertriglyceridemia.

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13. The method of claim 12, wherein the therapeutically effective amount of the additional form of treatment when administered in combination with a compound of the invention is less than the amount of the additional form of treatment that would be therapeutically effective if delivered to the patient alone.

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14. The method of claim 12, wherein the additional form of treatment is insulin.

15. The method of claim 12, wherein the additional form of treatment is an insulin analog.

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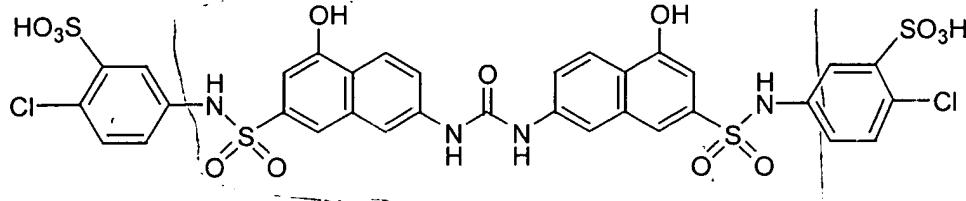
16. The method of claim 14, wherein the therapeutically effective amount of insulin or insulin analog when administered in combination with a compound of the invention is less than the amount of insulin or insulin analog which would be therapeutically effective if delivered to the patient alone.

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17. The method of claim 1, comprising administering two of the compounds of claims 3-11.

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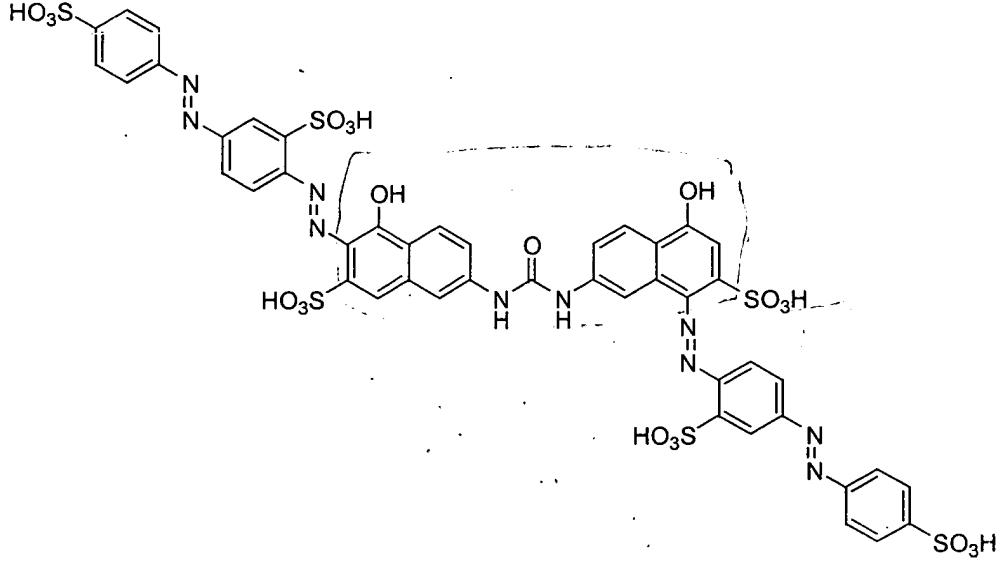
18. The method of claim 1, where the insulin receptor-activating compound is



or a pharmaceutically acceptable salt thereof.

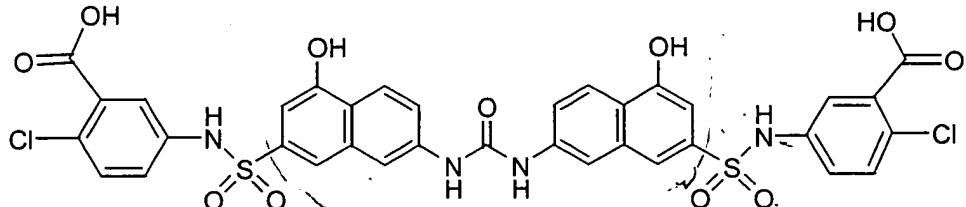
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19. The method of claim 1, where the insulin receptor-activating compound is



or a pharmaceutically acceptable salt thereof.

10 20. The method of claim 1, where the insulin receptor-activating compound is



or a pharmaceutically acceptable salt thereof.

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